Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

COVID-19 vaccines surveillance in France: a global response to a major national challenge

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SARS-CoV-2 is a coronavirus responsible of COVID-19 disease, an acute respiratory infection that can be serious and lead to death in certain population categories with comorbidities. SARS-CoV-2 infection has rapidly spread to become a global pandemic since early 2020. From this period and for almost a year, barrier measures have constituted the sole effective tool for the prevention of disease transmission.

By the end of 2020, the first COVID-19 vaccine based on mRNA has been authorised by the European Medicines Agency. To date, three vaccines are available in Europe and used in France: two mRNA vaccines (Comirnaty BioNTech-Pfizer, Moderna Vaccine) and one adenovirus vaccine (AstraZeneca Vaccine); a fourth one has been authorised and will be available in the coming weeks (Janssen vaccine). The efficacy of the vaccines has been demonstrated in clinical trials to prevent developing severe COVID-19 disease. Nowadays, the vaccines are considered as the best response against this pandemic crisis [1–4].

Monitoring COVID-19 vaccines is a major challenge, in particular to verify their effectiveness in the general population as well as to identify any adverse reactions (ADRs) that may not have been observed in clinical trials. Indeed, at the time of marketing, all the ADRs related to a drug are not known, specifically rare or delayed ADRs as well as those occurring in specific subpopulations (elderly, immunosuppressed or immunocompromised patients…). The usual challenge of this real-life monitoring and ADR detection was of even greater importance in the case of COVID-19 vaccines, for which each new day was to correspond to hundreds of thousands of additional individuals exposed to the drug.

French health drugs regulatory authority (ANSM) is in charge of the assessment of the vaccines safety by ensuring continuous monitoring of all ADRs, whether foreseeable or unexpected. This surveillance is based on the analysis of ADRs reported by healthcare professionals and patients to the national pharmacovigilance system, as well as to the European one, on the achievement of pharmaco-epidemiology studies and on the support for research projects through funding.

As part of the national COVID-19 vaccination campaign, ANSM put in place a specific strengthened surveillance system for the ADRs COVID-19 vaccines on French territory, which is integrated to the risk management plan coordinated by the European Medicines Agency. The objectives are to carry out a continuous assessment COVID-19 vaccines safety in order to be able to detect early potential safety issues and take rapid relevant risk minimisation measures. Furthermore, this specific surveillance provides relevant information allowing the Ministry of Health to adapt the vaccination strategy, if necessary.

This specific strengthened surveillance system had four complementary components.

First, ANSM has mobilised the French Network of regional pharmacovigilance centres (CRPV) to ensure continuous monitoring and assessment of COVID-19 vaccines ADRs through the daily assessment of spontaneous reports. Healthcare professionals or users can report potential ADRs following vaccination directly to the regional pharmacovigilance centre or using a dedicated web portal [5]. To facilitate the reporting of potential ADRs and in particular those serious and/or unexpected, ANSM provided health professionals and vaccinated people with specific and pedagogic guidelines. Each report of potential ADRs is assessed through a careful clinical, chronological, semiological and pharmacological analysis before being entered into a centralised French pharmacovigilance database. This often requires the pharmacologist from the regional pharmacovigilance centre to complete the information initially reported by contacting the reporter/the hospital in which the patient was admitted. In the perspective of high volume of reporting, supplementary funding was allocated to the pharmacovigilance centre so that they could hire temporary additional staff.

Second, based on these French nationwide spontaneous reporting data, a pharmacovigilance intensive survey was set up. Six experts from regional pharmacovigilance centres were nominated to establish weekly pharmacovigilance reports for each of the first three marketed COVID-19 vaccines (two to three experts were nominated for each vaccine). This exceptional involvement makes possible to monitor in real time the safety profile of vaccines in the vaccinated population based on the reported potential ADRs.

Third, a scientific monitoring committee was set-up that would collegially evaluate the reports delivered on a daily basis. This

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scientific monitoring committee was constituted from ANSM staff members, the pharmacovigilance experts in charge of the survey, and pharmacovigilance experts with specialised medical expertise (*e.g.*, cardiology, neurology, dermatology/immuno-allergology). During the committee weekly meetings, a crosschecking of safety signals, in particular from clinical trials, scientific literature, European and international data and statistical monitoring of the national pharmacovigilance database would be discussed. If a safety signal was validated, appropriate measures would be issued in relation with the European Medicines Agency. These measures will aim to manage and minimise the risk potentiality in vaccinated people.

A communication plan was associated to this strengthened surveillance system. On a weekly basis, ANSM publishes on its website the vaccines monitoring pharmacovigilance survey reports as well as a summary sheet integrating the key figures of pharmacovigilance data and the outstanding results [6].

As of the 18th of March 2021, a total of 17 104 reports have been collected and analysed: 10 963 for Comirnaty (BioNTech-Pfizer), 458 for COVID-19 Vaccine Moderna and 5 683 for COVID-19 Vaccine AstraZeneca. The reporting rate varies between 1.0 and 3.9 reports per 1 000 doses administrated.

For all three vaccines, the majority of reports is common to most other vaccines and concerns erythema and pain at the injection site, headache, myalgia, chills, fatigue, nausea, fever, dizziness and weakness as shown by phase 3 clinical trials.

For Comirnaty vaccine [7], the reports are mostly non-serious (78%). They concern women for 74% of the total. Most of them (53%) were related to persons aged 50-64 years old. Regarding the reported cases of death, current data do not lead to the conclusion that they are related to vaccination. Seventy-two per cent of ADRs occurred 24 hours after the vaccination. A total of five safety signals (Table 1) related to Comirnaty have been detected thanks to this pharmacovigilance survey: arterial hypertension, cardiac arrhythmias, Herpes zoster infection, thrombocytopaenia/immune thrombocytopaenia/spontaneous haematomas, diabetic complications (hyperglycaemia, hypoglycaemia). A total of 274 severe arterial hypertension reactions, with immediate or delayed onset after vaccination, were collected, occurring immediately or delayed after vaccination. The ADRs outcome resolves in a few hours to a few days, spontaneously after medical supervision, or after initiation or adaptation of the antihypertensive treatment. A total of 124 severe reports of cardiac arrhythmias (*e.g.*, tachycardia, atrial fibrillation, atrial flutter, and bradycardia) have been collected. They mostly occur shortly after the vaccination but some are delayed (some days after). One hundred and fifty-six reports of herpes zoster infection have been collected, some of which occurred in a context of reactogenicity or as a result of the effects of reactogenicity. Two-thirds of them occurred during the first week after the vaccination. Finally, a large number of cases of systemic reactogenicity corresponding to flu-like syndromes (fever, myalgia, chills) have been reported after the second dose of Comirnaty vaccine, which is consistent with clinical trial data. They must nevertheless lead to notice that more significant reactogenicity happen with the second dose. Seven cases of thrombocytopaenia/immune thrombocytopaenia were observed. These adverse effects occur within less than 8 days. Although the data are still limited, the occurrence of a case with recurrence after the second injection leads to evoke a potential signal. A total of 16 cases of diabetes inadequate control/hyperglycaemia were reported. Furthermore, the effects of hypersensitivity and anaphylaxis appear to date less frequently after the second dose. No reports of cerebral venous thrombosis or disseminated intravascular coagulation associated or not with thrombocytopaenia have been reported in France with Comirnaty vaccine.

Concerning the Moderna vaccine [8], the reports are mostly (84%) non-serious, and mainly concern women up to 76%. Fifty per cent of the reports were related to persons aged 75-84 years old. The reports correspond mostly (n = 344, 75%) to a non-serious local or systemic reactogenicity and resolve quickly without

Table 1

	Adverse Reaction Reporting rate Per 1000 doses	Number of doses administered	Serious/Non-serious ADRs report	Events under specific monitoring	Potential or confirmed signals
Comirnaty (BioNTech-Pfizer)	1.7	6 282 094	27%/73%	- Pericarditis - Aortic dissection - Convulsions - Reactions with a known history of infection with COVID-19 -Hypersensitivity/anaphylaxis and asthma - Facial paralysis - Anosmia/ageusia - Vestibular disorders - Hearing problems - Vasculitis	- Arterial hypertension - Cardiac arrhythmias - Herpes zoster infection - Thrombocytopaenia/immune thrombocytopaenia/spontaneous haematomas - Diabetic complications
COVID-19 Vaccine Moderna	1.0	441 160	16%/84%	- Arterial hypertension - Cardiac arrhythmias - Herpes zoster infection - Second dose reactogenicity	None
COVID-19 Vaccine AstraZeneca	3.9	1 430 790	27%/73%	- Hypertension - Exacerbations of dyspnoea and asthma -Non-infectious encephalitis - Cardiac arrhythmias and conduction disorders - Anaphylactic reactions/Urticaria - Hypotension - Hypothermia - Lymphopaenia - Diabetic imbalances - Myopericarditis/pericarditis - Epistaxis	- Influenza-like symptoms - Thrombosis in large veins (cerebral in majority, but also digestive), which may be associated with thrombocytopaenia or coagulation disorders

outcome. The number of delayed reactions that may occur from 7 to 16 days after vaccination is more significant than previously described in the clinical trial Cove. These non-serious reactions occur at the site of vaccination. We also observe as for Comirnaty, some cases of vascular disorders such as arterial hypertension and arrhythmias (N = 19 and 6 respectively). Reports (n = 12) of herpes zoster infection have also been collected; these ADRs will be the subject of special monitoring. No cases of cerebral venous thrombosis or disseminated intravascular coagulation associated or not with thrombocytopaenia have been reported in France. To date, there is no safety signal with the Moderna vaccine (Table 1).

For AstraZeneca vaccine [9], the reports are mostly non-serious (73%). They concern women for 76% of the total. Most of the reports (79%) were related to persons aged 16-49 years old. Among the reported cases, a large number of cases correspond to influenza-like illnesses, some are very severe, that occur mostly (71%) within 24 hours. There are also cases of dyspnoea associated with influenza-like syndromes (n = 39) and cases of asthma exacerbation (n = 3). Fifteen serious cases of hypertension occurred outside of a context of reactogenicity including 4 responsible for neurological complications. These ADRs need more investigations. It was detected a safety signal (Table 1) concerning AstraZeneca vaccine, which concerns severe influenza-like symptoms. This leads to have an agile and sequenced organisation of collective vaccination such as healthcare professionals in a hospital. Nine cases of thrombosis in the large veins (mostly cerebral, but also digestive), which may be associated with thrombocytopaenia or coagulation disorders, have been reported. These cases, describing a new symptomatology, occur in a median time of 8.5 days after vaccination (7 patients $<$ 55 years old, 2 patients over 55 years old) without a specific pattern identified to date, apart from an oral contraception for 3 cases, associated with a protein C/S deficiency in a fourth. Among them, two had a fatal outcome. The very atypical nature of these thromboses, their common clinical characteristics and homogeneous time to onset lead us to confirm the signal of this very rare thrombotic risk. A review of thromboembolic events is being conducted at the European Medicines Agency to provide additional input, such as plausible mechanism of action, possible underlying risk factors and any additional data needed to gain a deeper understanding of the observed events and the potential risk.

Conflicts of interest

The authors have no conflicts of interest to declare.

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